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(54) Title: ASSAYS RELATING TO TOLL-LIKE RECEPTOR ACTIVITY

(57) Abstract: The present invention provides assays useful for detecting agonists of Toll-like receptors. The assays include providing a cell culture transfected with a nucleic acid sequence that encodes a reporter operably linked to a TLR-inducible expression control sequence.

ASSAYS RELATING TO TOLL-LIKE RECEPTOR ACTIVITY

Background of the Invention

Cells of the immune system secrete a diverse set of compounds including cytokines, chemokines, co-stimulatory markers, and defensins in response to an immunological challenge.

Certain compounds known as immune response modifiers ("IRMs") possess potent immunostimulating activity including but not limited to antiviral and antitumor activity. Certain IRMs effect their immunostimulatory activity by, e.g., inducing the production and secretion of certain cytokines while inhibiting production and secretion of other cytokines. Certain IRMs are small organic molecules such as those disclosed in, for example, U.S. Patent Nos. 4,689,338; 4,929,624; 5,266,575; 5,268,376; 5,352,784; 5,389,640; 5,482,936; 5,494,916; 6,110,929; 6,194,425; 4,988,815; 5,175,296; 5,367,076; 5,395,937; 5,693,811; 5,741,908; 5,238,944; 5,939,090; 6,245,776; 6,039,969; 6,083,969; 6,245,776; 6,331,539; and 6,376,669; and PCT Publications WO 00/76505; WO 00/76518; WO 02/46188, WO 02/ 46189; WO 02/46190; WO 02/46191; WO 02/46192; WO 02/46193; and WO 02/46194.

Additional small molecule IRMs include purine derivatives (such as those described in U.S. Patent Nos. 6,376,50 and 6,028,076), small heterocyclic compounds (such as those described in U.S. Patent No. 6,329,381), and amide derivatives (such as those described in U.S. Patent No. 6,069,149).

Other IRMs include large biological molecules such as oligonucleotide sequences. Some IRM oligonucleotide sequences contain cytosine-guanine dinucleotides (CpG) and are described, for example, in U.S. Patent Nos. 6,1994,388; 6,207,646; 6,239,116; 6,339,068; and 6,406,705. Other IRM nucleotide sequences lack CpG and are described, for example, in International Patent Publication No. WO 00/75304.

Some of these IRMs induce cellular responses (e.g., the production and/or secretion of cytokines, chemokines, etc.) through one or more Toll-like receptors (TLRs). For example, certain small organic molecule IRMs are agonists of one or more of TLR-1, TLR-2, TLR-4, TLR-6, TLR-7, and TLR-8. Additionally, CpG has been reported to act through TLR 9.

In certain cells of the immune system, TLR activation can be associated with activation of the transcription factor NF-κB. NF-κB activation is associated with certain cellular responses to an immunological challenge, such as the production and secretion of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8, IL-10, IL-12, MIP-1, and MCP-1. IRM induction of such cellular responses can be demonstrated by measuring activation of the transcription factor NF-κB in response to exposing a cell to an IRM compound (See, e.g., Chuang *et al.*, *Journ. of Leuk. Biol.*, vol. 71, pp. 538-544 (2002), and Hemmi *et al.*, *Nature Immunology*, vol. 3(2), pp. 196-200 (2002)). Thus, NF-κB activation can be used as a reporter of TLR activation. However, the extent of NF-κB activation does not necessarily correlate with the extent of the downstream cellular response. This is so because the downstream cellular response may be modulated by one or more additional factors.

Summary of the Invention

The present invention provides assays for detecting activation of a TLR. The assays include providing a cell culture comprising cells transfected with a nucleic acid sequence that encodes a reporter that (a) generates a detectable signal when the reporter is expressed and the cell is exposed to conditions effective for generating the detectable signal, and (b) is operably linked to an expression control sequence that is induced by activation of a TLR and comprises a cytokine promoter, a chemokine promoter, a co-stimulatory marker promoter, or a defensin promoter; exposing the cell culture to a compound that activates a TLR; providing conditions effective for generating the detectable signal; and detecting the detectable signal.

In another aspect, the present invention provides assays for identifying agonists of a TLR. The assays include providing a cell culture comprising cells transfected with a first nucleic acid sequence that comprises a nucleotide sequence that encodes a TLR operably linked to a first expression control sequence, and a second nucleic acid sequence that encodes a reporter that (a) generates a detectable signal when the reporter is expressed and the transfected cell is exposed to conditions effective for generating the detectable signal, and (b) is operably linked to a second expression control sequence that is induced by activation of a TLR; contacting the cell culture with a test compound; providing conditions effective for generating the detectable signal, thereby generating a TLR-

mediated detectable signal; and identifying the compound as an agonist of the TLR if a TLR-mediated detectable signal is detected.

In another aspect, the present invention provides assays for identifying antagonists of a TLR. These assays include providing a cell culture that comprises cells transfected with a first nucleic acid sequence that comprises a nucleotide sequence that encodes the TLR operably linked to a first expression control sequence, and a second nucleic acid sequence that encodes a reporter that (a) is operably linked to a second expression control sequence that is induced by activation of a TLR, and (b) generates a detectable signal when the reporter is expressed and the transfected cell is exposed to conditions effective for generating the detectable signal; contacting the cell culture with an agonist of the TLR and a test compound; providing conditions effective for generating the detectable signal, thereby permitting the cell culture to generate a full TLR-mediated detectable signal in the absence of an antagonist of the TLR; measuring the detectable signal; and identifying the compound as an antagonist of the TLR if the detectable signal is less than a full TLR-mediated detectable signal.

In another aspect, the present invention provides a TLR agonists and TLR antagonists identified using an assay according to certain embodiments of the present invention.

In yet another aspect, the present invention provides pharmaceutical compositions including a TLR agonist or a TLR antagonist identified using an assay according to certain embodiments of the present invention.

Various other features and advantages of the present invention should become readily apparent with reference to the following detailed description, examples, and claims. In several places throughout the specification, guidance is provided through lists of examples. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

Detailed Description of Illustrative Embodiments of the Invention

The present invention provides assays that may be useful for detecting TLR activation based on detecting induction of a downstream cellular response to TLR activation (e.g., production or secretion of one or more immune system compounds such as cytokines or co-stimulatory markers) rather than NF-κB activation. In some cases, the

cellular response may be mediated by NF-κB, but in other cases the cellular response may be NF-κB-independent. Thus, the present invention provides assays that may be useful for detecting a broader range of TLR activation than is possible by monitoring NF-κB activation. This may provide an ability to identify certain TLR agonists that would not be detected using an assay based on NF-κB activation. The assays of the present invention also may provide a more relevant indication of the quantitative character of a particular cellular response to TLR activation by a particular TLR agonist.

In some cases, an assay according to the present invention may be useful for detecting TLR activation that is not accompanied by NF-κB activation. Such an assay may be employed to identify TLR agonists that do not necessarily also activate NF-κB. Such TLR agonists may be useful for treatment or prevention of certain conditions in which the production and secretion of pro-inflammatory cytokines such as those induced by NF-κB activation may be undesirable.

For purposes of this invention, the following terms shall have the meanings set forth.

"Activation" refers to modifying the indicated protein so that the protein provides a biological function. For example, TLR activation refers to modifying a TLR, such as in response to exposure of the TLR to an agonist, so that the TLR is capable of inducing the production and secretion of certain cytokines.

"Agonist" refers to a compound that can combine with a receptor (e.g., a TLR) to produce a cellular response. An agonist may be a ligand that directly binds to the receptor. Alternatively, an agonist may combine with a receptor indirectly by, e.g., (a) forming a complex with another molecule that directly binds to the receptor, or (b) otherwise results in the modification of another compound so that the other compound directly binds to the receptor. An agonist may be referred to as an agonist of a particular TLR (e.g., a TLR6 agonist).

"Amino acid sequence" refers to a particular ordered sequence of amino acids, whether naturally occurring or engineered.

"Antagonist" refers to a compound that can combine with a receptor (e.g., a TLR) to inhibit a cellular response. An antagonist may be a ligand that directly binds to the receptor. Alternatively, an antagonist may combine with a receptor indirectly by, e.g., (a) forming a complex with another molecule that directly binds to the receptor, or (b)

otherwise results in the modification of another compound so that the other compound directly binds to the receptor. An antagonist may be referred to as an antagonist of a particular TLR (e.g., a TLR6 antagonist). An antagonist may inhibit biological activity to any measurable extent.

"Co-transfect" and variations thereof refer to transfecting a host cell with more than one vector. A host cell may be co-transfected by transfecting with two or more vectors one at a time or in any convenient combination of vectors, including simultaneous transfection with all vectors.

"Express/expression" refers to the ability of a cell to transcribe a structural gene to mRNA, then translate the mRNA to synthesize a protein that provides a detectable biological or biochemical function. "Expressible" refers to the ability of a particular nucleic acid sequence to be expressed by a cell that contains the nucleic acid sequence.

"Immune system compound" refers to any compound that is produced or secreted by cells of the immune system in response to an immunological challenge. Immune system compounds include but are not limited to cytokines, chemokines, co-stimulatory markers, and defensins.

"Inhibit" refers to any measurable reduction of biological activity.

"IRM compound" refers to a compound that alters the level of one or more immune system compounds when administered to an IRM-responsive cell. Representative IRM compounds include the small organic molecules, purine derivatives, small heterocyclic compounds, amide derivatives, and oligonucleotide sequences described above.

"Nucleic acid sequence" refers generally to a region of DNA that has a definable function such as (a) encoding a peptide, polypeptide, or protein or (b) controlling expression of a nucleic acid sequence that encodes a peptide, polypeptide, or protein. For example, a nucleic acid sequence that encodes TLR6 refers generically to any sequence of nucleotides that encodes a TLR6 protein, without regard to (a) the species source of the nucleic acid sequence, (b) specific nucleotide sequence variants, or (c) whether such nucleotide sequence variants are naturally occurring or engineered.

"Nucleotide sequence" refers to a particular ordered sequence of nucleotide bases, whether naturally occurring or engineered.

"TLR-mediated detectable signal" refers to a detectable signal or that portion of a detectable signal that is attributable to activation of a TLR expressed from a gene expression system transfected into a host cell. For example, a host cell may naturally generate a background level detectable signal (S_0), but generate a greater detectable signal (S_T) after being transfected with, and then expressing, a nucleic acid sequence that encodes a TLR. Thus, the TLR-mediated detectable signal (S_{TLR}) refers to the portion of the detectable signal generated by the transfected cell that is greater than background: $S_{TLR} = S_T - S_0$.

It has been found that induction of certain secreted proteins or polypeptides can be useful as reporters of TLR activation. For example, IFN-α is a cytokine secreted by such immune system cells as T lymphocytes, macrophages, plasmacytoid monocytes, dendritic cells, and natural killer cells. IFN-α is involved in regulating a host's innate and adaptive immune responses to an immunological challenge, perhaps by providing a link between the two responses [Brassard *et al.*, *Journal of Leukocyte Biology* 71: 565-581 (2002)]. The innate immune response can include the cell-mediated response of natural killer (NK) cells to a non-self (e.g., neoplastic) or foreign (e.g., viral) antigen. IFN-α also may indirectly regulate the balance between Th1 and Th2 cell populations and, therefore, the innate and adaptive immune responses. Moreover, induction of IFN-α is independent of NF-κB activation.

Additionally, the production and secretion of NF-κB-dependent cytokines can be useful as reporters of cellular responses resulting from immunological challenge. Detection and measurement of such cytokines may provide comparative qualitative data regarding a cell's response to immunological challenge that is more relevant to an investigator than NF-κB activation data.

Thus, the present invention relates to assays designed to detect induction of immune system compounds. Such assays also may be useful for identifying compounds that induce expression of immune system compounds through TLRs. Parts of the following description are provided in the context of IFN-α induction and detection. However, many of the features of the embodiments described below also may be realized using assays designed to specifically detect or induce other immune system compounds. Thus, assays designed to specifically detect or induce other immune system compounds

having publicly available gene sequence information are explicitly included in the scope of the present invention.

Assay Tools

The assays of the present invention employ a recombinant cell line capable of inducing gene expression from an expression control sequence of a gene that encodes an immune system compound (e.g., IFN-α) in response to TLR activation. In some embodiments, for example, cells of the recombinant cell line, when exposed to a TLR agonist, can induce expression from an IFN-α promoter to a greater extent than cells of the corresponding untransfected cell line. Cells of the untransfected cell lines may substantially lack a functional level of TLR expression (i.e., untransfected cells may not detectably induce expression from the IFN-α promoter in response to exposure to a TLR agonist). Alternatively, cells of the untransfected cell line may exhibit a baseline level of background TLR function, but the baseline level is less than the level of TLR function observed in cells of the corresponding recombinant (i.e., transfected) cell line.

Cells of certain recombinant cell lines include a first nucleic acid sequence that encodes a TLR operably linked to an expression control sequence. The cells also include a second nucleic acid sequence that encodes a reporter capable of generating a detectable signal when it is expressed in the recombinant cell under conditions suitable for generating the detectable signal. The reporter is linked to a second expression control sequence that is capable of being induced by activation of the TLR encoded by the first nucleic acid sequence.

The TLR encoded by the first nucleic acid sequence, when present, may be any TLR. Ten different human TLRs have been identified, cloned, and sequenced. TLRs also are known to exist in other mammals including mice and chimpanzees. The nucleotide sequences of the ten human TLRs and many non-human TLRs are known, have been published, and are readily accessible from various sequence databases including GenBank. The first nucleic acid sequence may include any one of the TLRs for which the nucleotide sequence is known, whether human or non-human. In one embodiment, the TLR is human TLR6; in another embodiment, the TLR is human TLR7. Alternatively, the first nucleic acid may encode any one of the ten human TLRs, any non-human TLR, or any combination of two or more TLRs that may be desirable for a particular construct.

The first nucleic acid sequence, when present, can include a nucleotide sequence that differs from the specific published nucleotide sequence for the TLR encoded by the first nucleic acid sequence. For example, the first nucleic acid sequence can contain one or more substitutions (compared to a published TLR nucleotide sequence) that do not alter the amino acid sequence of the TLR protein expressed from the first nucleic acid sequence. Such a substitution may be termed a degenerate substitution. Nucleotide sequences containing one or more degenerate substitutions compared to a known TLR nucleotide sequence are explicitly included within the scope of nucleotide sequences suitable for use within the first nucleic acid sequence.

As another example, certain nucleotide substitutions may alter the amino acid sequence of the TLR protein. For certain amino acid substitutions, however, the chemical properties of the protein having the altered amino acid sequence are similar to the chemical properties of the protein having the native amino acid sequence. Amino acids may be divided into four groups based on the chemical characteristics of the amino acid side groups: neutral, non-polar amino acids include glycine, alanine, valine, isoleucine, leucine, phenylalanine, proline, and methionine; neutral, polar amino acids include serine, threonine, tyrosine, tryptophan, asparagine, glutamine, and cysteine; acidic amino acids include aspartic acid and glutamic acid; and basic amino acids include lysine, arginine, and histidine. Substitution of one amino acid for another amino acid within the same group may have little or no functional effect on the resulting protein because of the similarity of the chemical characteristics of the amino acids involved in the substitution. Such amino acid substitutions may be termed a conservative amino acid substitution. Nucleotide sequences that, when compared to a known TLR nucleotide sequence, generate one or more conservative amino acid substitutions are explicitly included within the scope of nucleotide sequences suitable for use within the first nucleic acid sequence.

The nucleic acid sequence that encodes a TLR, if present, may be cloned into an expression vector so that it is under the expression control of its own promoter, a homologous TLR promoter, or any heterologous promoter inducible in an appropriate host cell. For example, in certain embodiments, the TLR6 structural gene may be cloned into the commercially available mammalian expression vector pCI-neo. In this case, the TLR6 structural gene may be cloned into the vector's cloning region using the NheI and MluI restrictions sites. In such an embodiment, after transfection of the vector into a

mammalian cell, the TLR6 structural gene is under the transcriptional control of the vector's CMV enhancer/promoter region.

The second nucleic acid sequence encodes a reporter that is capable of generating a detectable signal when expressed in a host cell under conditions appropriate for generating the desired detectable signal. A wide variety of suitable reporter systems are known. For example, luciferase gene expression may generate a detectable luminescent signal under appropriate conditions. As another example, β-galactosidase expression can generate a detectable color change under appropriate conditions. As yet another example, production and secretion of an immune system compound may be detected by an enzyme-linked immunosorbent assay (ELISA). These and other reporter systems are known and assays for generating the detectable signals are commercially available.

The second nucleic acid sequence is operably linked to a second expression control sequence that includes a promoter sequence selected to be inducible by activation of a TLR. Thus, expression and activation of a TLR, whether naturally expressed by the recombinant cell or encoded by the first nucleic acid sequence, will induce gene expression from the second expression control sequence, thereby causing expression of the reporter, which may be detected by performing an assay designed to detect expression of the reporter. The second expression control sequence may include any suitable nucleotide sequence that can induce expression (e.g., a promoter) of a structural gene upon activation of the TLR encoded by the first nucleic acid sequence. Nucleotide sequences suitable for use as second expression control sequences include promoter sequences of TLR-inducible genes including but not limited to genes encoding cytokines, chemokines, co-stimulatory markers, and defensins. In certain embodiments, the second expression control sequence includes an IFN-α1 promoter.

When the reporter system being employed to detect TLR activation includes detecting production and secretion of an immune system compound with an appropriate ELISA assay, the second expression control sequence may include the promoter of the gene encoding the immune system compounds being expressed and detected as the reporter. However, in certain embodiments, it may be desirable to express the immune system compound from a heterologous promoter.

When the gene expression system includes both a first nucleic acid sequence and a second nucleic acid sequence, the first nucleic acid sequence and the second nucleic acid

sequence may be contained within a single vector. Alternatively, the first nucleic acid sequence and the second nucleic acid sequence may be on separate vectors and co-transfected into a suitable host cell. In certain embodiments, for example, the first nucleic acid sequence may be cloned into the pCI-neo vector as described above, while the second nucleic acid sequence can be cloned into a reporter vector. One example of a commercially available reporter vector is the pGL3-Enhancer vector, which includes a luciferase reporter gene downstream of a cloning site for cloning a promoter sequence of interest. In some embodiments, the promoter of a TLR-inducible immune system compound may be cloned into the pGL3-Enhancer cloning site. In one such embodiment, the IFN-α promoter may be cloned into the pGL3-Enhancer cloning site.

Suitable host cells include any transfectable cells capable of expressing exogenous mammalian genes. In some embodiments, the host cells may be mammalian cells such as human cells or mouse cells. For example, suitable host cells include human cells or descendants of a human cell including but not limited to Namalwa cells or HEK293 cells. Alternatively, the host cells may be mouse cells or descendants of a mouse cell including but not limited to RAW 264.7 cells.

In one embodiment, the host cells include Namalwa cells. Namalwa cells have certain characteristics that may be particularly desirable for certain embodiments of the present invention. For example, Namalwa cells can include an expressible chromosomal IFN-α gene locus. Thus, upon appropriate stimulation (e.g., viral infection), Namalwa cells can be induced to produce and secrete IFN-α from the chromosomal IFN-α gene locus. However, Namalwa cells do not naturally express certain TLRs (e.g., TLR6, TLR7, or TLR9). Certain agonists of such TLRs have been shown to induce IFN-α expression in other cell types (e.g., PMBCs), but may not induce IFN-α expression in Namalwa cells unless a functional level of TLR expression is provided.

Namalwa cells transfected with an appropriate gene expression system may be capable of expressing a functional level of the TLR provided by the expression system. Thus, Namalwa cells transfected with an appropriate expression system may inducibly express IFN-α as a result of activating the cloned TLR (e.g., by exposure of the transfected Namalwa cells to an agonist). Thus, certain transfected cell lines permit one to identify a TLR agonist using an assay that detects TLR-mediated IFN-α expression by Namalwa cells.

Namalwa cells transfected with certain expression systems can provide alternative means of detecting TLR activation and, therefore, alternate assays for identifying TLR agonists. First, Namalwa cells transfected with an appropriate expression system may generate a detectable signal as a result of TLR-mediated expression of the expression system reporter (see Table 2). Second, Namalwa cells transfected with an expression system that provides functional TLR activity may provide TLR-mediated IFN-α expression from the chromosomal IFN-α gene locus.

Assays

Assays according to the present invention may be performed using any suitable recombinant cell line. The recombinant cell line may be constructed by transfecting any suitable expression system into any suitable host cell. In the description of particular assays that follow, certain assay tools such as particular recombinant cell lines, particular gene expression systems, or particular host cells may be identified. However, many alternative assay tools may provide the features of the tools specifically identified and, consequently, may be suitable for use in assays according to the present invention. Such alternative embodiments are explicitly included in the scope of the present invention.

Also, each assay may or may not be performed in conjunction with one or more appropriate controls. Controls may be performed to assist in quantifying results or to ensure that the assay is performing as intended. However, with experience, one skilled in the art may develop sufficient familiarity with a particular assay that performing a control may not always be necessary to perform an assay of the present invention.

In some embodiments, assays according to the present invention may be designed to detect activation of a TLR. Such assays include providing a recombinant cell line having an appropriate gene expression system. Generally, an appropriate gene expression system includes a reporter that is (a) capable of generating a detectable signal when the reporter is expressed and the transfected cell is exposed to conditions that are appropriate for generating the detectable signal, and (b) operably linked to an expression control sequence that is capable of being induced by an activated TLR. The assays also include exposing the recombinant cell line to a TLR agonist, thereby activating the TLR and inducing expression of the reporter from the TLR-inducible expression control sequence; providing conditions appropriate for generating the reporter's detectable signal, thereby

generating a detectable signal from the expressed reporter; and detecting the detectable signal, thereby detecting activation of the TLR.

In certain embodiments, the expression control sequence to which the reporter is operably linked may be a promoter of a TLR-inducible protein including but not limited to a cytokine, a chemokine, a co-stimulatory marker, or a defensin.

The recombinant cell line may be derived from a host cell that naturally expresses a functional level of one or more TLRs. In such embodiments, the gene expression system is not required to include a nucleic acid sequence that encodes a TLR. However, the gene expression system may include a nucleic acid sequence that encodes a TLR. For such assays, it may be desirable to measure any background level of detectable signal generated by the recombinant cell line before transfection with the nucleic acid sequence that encodes the TLR. In this way, one can obtain an indication of the extent of the detectable signal that is attributable to activation of the TLR expressed from the expression system if such an indication is desired.

When the gene expression system includes a nucleic acid sequence that encodes a TLR, one may select any TLR from any species for inclusion in the expression system. Accordingly, the nucleic acid sequence that encodes the TLR may include any one of the published TLR nucleotide sequences, any nucleotide sequence containing one or more degenerate variants of a published TLR nucleotide sequence, any nucleotide sequence that encodes a published TLR amino acid sequence, or any nucleotide sequence that encodes a protein having one or more conservative amino acid substitutions compared to a published TLR amino acid sequence.

In some embodiments in which the recombinant cell line includes a nucleic acid sequence encoding a TLR, a single vector may contain a first nucleic acid sequence that encodes the reporter and a second nucleic acid sequence that encodes the TLR. Alternatively, the first nucleic acid sequence and the second nucleic acid sequence may exist on separate vectors so that the host cells must be co-transfected with both vectors in order for the recombinant cell line to include entire gene expression system.

The gene expression system may include any suitable reporter operably linked to any suitable TLR-inducible expression control sequence. Suitable reporters are described in the detailed description of the gene expression system included in the description of assay tools provided above.

In one particular embodiment, the recombinant cell line is derived from the human lymphoblastoid Namalwa cell line. Namalwa cells lack a functional level of TLR6 activity. The recombinant cell line is obtained by co-transfecting Namalwa cells with two vectors that, together, provide a gene expression system: the first vector includes a nucleic acid sequence that encodes human TLR6 operably linked to an expression control sequence; the second vector contains a nucleic acid sequence that encodes a luciferase reporter gene that is operably linked to an IFN-α promoter. The IFN-α promoter is inducible by activation of TLR6. A culture of the recombinant cells is contacted with an agonist of TLR6, thereby activating TLR6 that has been expressed from the first vector of gene expression system. The activation of TLR6 induces expression from the IFN-α promoter on the second vector of the gene expression system. Expression from the IFN-α promoter results in expression of the luciferase reporter gene. The recombinant cells, which are now expressing the luciferase reporter, are contacted with a luciferase reagent that generates a luminescent signal when allowed to react with luciferase. Detection of the luminescent signal indicates expression of the luciferase reporter from the IFN-α promoter that, in turn, indicates activation of TLR6.

As indicated above in the detailed description of the assay tools, various suitable reporter systems may be used in alternative embodiments of assays according to the present invention. Also as indicated above, one feature of constructing the recombinant cell line from Namalwa host cells is the cells can produce and secrete IFN-α expressed from the chromosomal IFN-α gene locus of the Namalwa cell. Thus, detection of IFN-α production (e.g., by ELISA) may be used as a reporter of TLR activation. When used in conjunction with a reporter encoded by the gene expression system, the use of two independent reporters may provide certain embodiments of the assays of the present invention with an internal control.

In some alternative embodiments, assays according to the present invention may be designed to identify agonists of a particular TLR. Generally, such assays include providing a recombinant cell line constructed by transfecting host cells with a gene expression system that includes (a) a first nucleic acid sequence that encodes a particular TLR, and (b) a second nucleic acid sequence that encodes a reporter operably linked to an expression control sequence that is inducible by activation of the TLR encoded by the expression system. The assays also include contacting cell cultures of the recombinant

cell line with one or more test compounds, and then exposing the cell cultures to conditions effective for generating a detectable signal from the reporter in the event that the reporter is expressed. Detection of a TLR-mediated detectable signal indicates that expression of the reporter is at least partially attributable to activation of the TLR by the test compound, thereby identifying the test compound as an agonist of the TLR.

As with the assays described above that are designed for detecting TLR activation, assays for detecting TLR agonists include a gene expression system that may include one or more vectors, a nucleic acid sequence that encodes any suitable reporter, and any suitable TLR-inducible expression control sequence. Furthermore, the gene expression system can include a nucleic acid sequence that encodes any particular TLR. Thus, an assay may be designed to identify agonists of any particular TLR.

Detection of a TLR-mediated detectable signal may include a determination of background detectable signal generated by the recombinant cell line prior to transfection with a nucleic acid sequence that encodes a particular TLR. A recombinant cell line may, in some embodiments, naturally possess a certain level of TLR expression that can induce expression of the reporter, thereby generating background signal. Alternatively, background expression of the reporter may result from induction of the expression control sequence that regulates expression of the reporter coming from an alternative (i.e., non-TLR) source. Once a background level of detectable signal is determined for the recombinant cell line, it may not be necessary to determine the background signal generation every time the assay is performed.

In one particular embodiment, the recombinant cell line includes Namalwa cells, cells that lack a functional level of natural TLR6 expression. The recombinant cell line is constructed by co-transfecting Namalwa cells with a gene expression system that includes two vectors: a first vector that includes a first nucleic acid sequence that encodes human TLR6 operably linked to an expression control sequence; and a second vector that includes a second nucleic acid sequence that encodes a luciferase reporter operably linked to an IFN-α promoter. The first nucleic acid sequence permits the recombinant cells to functionally express TLR6. The second nucleic acid sequence allows one to detect activation of the TLR6 expressed from the first nucleic acid sequence.

In this particular embodiment, a culture of the recombinant cells is dispensed into wells of a multi-well test plate. A different test compound is added to each well. A test

compound that acts as a TLR6 agonist will activate the TLR6 expressed from the first vector of the gene expression system, thereby inducing expression from the IFN-α promoter operably linked to the luciferase reporter on the second vector of the gene expression system. The recombinant cells, which are now expressing the luciferase reporter, are contacted with a luciferase reagent that generates a TLR-mediated detectable signal only when the luciferase reporter is expressed. Detection of a TLR-mediated detectable signal in a particular well of the multi-well plate indicates expression of the luciferase reporter from the IFN-α promoter that, in turn, indicates activation of TLR6 by the test compound added to the recombinant cells in that well. A test compound that activates TLR6 is an agonist of TLR6.

Test compounds may be added to wells containing recombinant cells in any manner appropriate for the design of a particular assay. For example, the same test compound may be added to each of a plurality of wells, thereby generating multiple data points for that test compound. Alternatively, a different test compound may be added to each well. In this way, the number of test compounds that can be screened in a single assay can be maximized. In some embodiments, test compound may even be omitted from a certain number of wells, e.g., in order to generate one or more controls.

In another particular embodiment, the assay may be designed to identify agonists of TLR7 by designing the recombinant cell line to include a gene expression system that includes a nucleic acid sequence that encodes human TLR7. In all other respects, the assay may be performed as described above for the detection of TLR6 agonists.

Additional alternative embodiments include assays that are designed to identify agonists of any one of the human TLRs or any non-human TLR merely by designing the gene expression system to include a nucleic acid sequence that encodes the desired TLR.

The present invention also provides TLR agonist compounds identified using an assay according to certain embodiments of the present invention. As described above, the expression systems and recombinant cell lines may provide the ability to design assays that can identify TLR agonists that are not detectable using previously known TLR activation assays. The TLR agonists may include chemical structures similar in certain respects to the chemical structures of known IRM compounds. Alternatively, assays according to the present invention may be used for screening (e.g., high throughput screening) chemically diverse compounds that may lead to the discovery of new TLR

agonists, some of which may contain new chemical core structures capable of activating TLRs.

The present invention also provides pharmaceutical compositions containing a TLR agonist identified using an assay according to the present invention, or a pharmaceutically acceptable salt thereof, in an amount effective for inducing a TLR-mediated cellular response.

In still other embodiments, assays according to the present invention may be designed to identify antagonists of a particular TLR. Generally, an assay may be designed to identify an antagonist of a particular TLR by designing the recombinant cell line to include a gene expression system having (a) a first nucleic acid sequence that encodes a particular TLR, and (b) a second nucleic acid sequence that encodes a reporter operably linked to a TLR-inducible expression control sequence. Aliquots of the recombinant cell line may be dispensed into wells of a multi-well test plate. A different test compound can be added to each well, and then a known agonist of the particular TLR can be added to each well. In such assays, the agonist of the particular TLR will induce expression of the reporter and generation of a detectable signal unless the test compound acts as an antagonist of the particular TLR. Therefore, antagonists of the particular TLR can be identified by detecting wells exhibiting something less than a full TLR-mediated detectable signal.

As with the assays described above that are designed for identifying TLR agonists, assays for detecting TLR antagonists include a gene expression system that may include one or more vectors, a nucleic acid sequence that encodes any suitable reporter, any suitable TLR-inducible expression control sequence, and a nucleic acid sequence that encodes any particular TLR. Thus, an assay may be designed to identify antagonists of any particular TLR.

In one particular embodiment, an assay that identifies antagonists of human TLR6 may be designed using the recombinant cell line described above for the identification of TLR6 agonists. The recombinant cells are dispensed into the wells of a multi-well test plate. A different test compound is added to each well. A known TLR6 agonist such as any one of the IRM compounds listed in Table 1 can be added to each well.

Generation and detection of the TLR-mediated detectable signal can be performed as described above for assays designed to detect TLR activation or identify TLR agonists.

The TLR-mediated detectable signal from each well can be compared to a standard full TLR-mediated detectable signal or to a positive control. Test compounds that inhibit the TLR-mediate detectable signal compared to the standard or the positive control can be identified as antagonists of TLR6.

In alternative embodiments, test compounds may be added to the wells in any desired manner, as described above with regard to assays designed to identify TLR agonists.

Other alternative embodiments include assays designed to identify antagonists of any one of the human TLRs or any non-human TLR. Such alternative embodiments may be performed by designing the gene expression system to include a nucleic acid sequence that encodes the desired TLR.

The present invention also provides TLR antagonist compounds identified using an assay according to certain embodiments of the present invention. As described above, the expression systems and recombinant cell lines may provide the ability to design assays that can identify TLR antagonists that are not detectable using previously known TLR activation assays. The TLR antagonists may include chemical structures similar in certain respects to the chemical structures of known IRM compounds. Alternatively, assays according to the present invention may be used for screening (e.g., high throughput screening) chemically diverse compounds that may lead to the discovery of new TLR antagonists, some of which may contain new chemical core structures capable of activating TLRs.

The present invention also provides pharmaceutical compositions containing a TLR antagonist identified using an assay according to the present invention, or a pharmaceutically acceptable salt thereof, in an amount effective for inhibiting a TLR-mediated cellular response.

Examples

The following examples have been selected merely to further illustrate features, advantages, and other details of the invention. It is to be expressly understood, however, that while the examples serve this purpose, the particular materials and amounts used as well as other conditions and details are not to be construed in a matter that would unduly limit the scope of this invention.

Construction of vectors

The vector pIFN-α1-luc was constructed by inserting BglII sites at both ends of the human IFN-α1 promoter (SEQ ID NO:21). The BglII sites were inserted into the IFN-α1 promoter and the sequence was amplified using the primer pair of SEQ ID NO:22 and SEQ ID NO:23. The amplified IFN-α1 promoter was cloned into the pGL3-Enhancing vector (Promega Corp., Madison, WI) at the BglII site.

The vector pCI-TLR6 was constructed by inserting SEQ ID NO:11 (GenBank Accession No. NM 006068), which includes the human TLR6 coding sequence, into the pCI-neo mammalian expression vector (Promega Corp.) at the vector's NheI and MluI restriction sites.

Transfections

Unless otherwise indicated, all incubations were performed at 37°C with 5% CO_2 at 98% humidity.

Culture medium was prepared from complete RPMI 1640 medium (BioSource International, Inc., Camarillo, CA). Fetal bovine serum (Atlas Biologicals, Inc., Ft. Collins, CO) was added to a final concentration of 7.5% (vol/vol); L-glutamine (BioSource International, Inc.) was added to 5 mM; and sodium pyruvate (BioSource International, Inc.) was added to 1 mM.

Burkitt's Lymphoma lymphoblastoid Namalwa cells (ATCC Accession No. CRL-1432) were grown by incubation in culture medium overnight. Cells were harvested by centrifugation in a tabletop centrifuge (1200 RPM for 5 minutes), and then resuspended in phosphate buffered sucrose to a concentration of 1.3×10^7 cells per milliliter.

For each transfection, a 750 μL aliquot of the cell suspension was placed in an electroporation cuvette with 4 mm gaps. 10 μg of the pIFN-α1-luc vector and 10 μg of the pCI-TLR6 vector were added to the electroporation cuvette. The cell and vector mixtures were incubated at room temperature for 5 minutes. The cells were electroporated using a BioRad Gene Pulser (BioRad Laboratories, Hercules, CA) set to at 500 μF capacitance and 0.27 volts, then incubated at room temperature for 5 minutes.

The electroporated cells were suspended in 10 mLs of culture medium and incubated overnight. Dead cells and debris were removed after 24 hours using a MACS

Dead Cell Removal kit (Miltenyi Biotec, Auburn, CA). Cells were resuspended in 10 mLs of culture medium and incubated for an additional 24 hours.

Transfected cells were selected by adding G418 (Promega Corp., Madison, WI) to a final concentration of 1 mg/mL and incubating the cells for seven days.

Assays

The selected transfected cells were counted and resuspended to a concentration of 1×10^6 cell per mL in culture medium. 100 μl aliquots of cells were placed in the wells of a white-walled, white-bottomed 96-well plate (Corning, Inc. Corning, NY). 1.0 μL of an IRM compound from Table 1 (prepared at 1 mM in 100% DMSO) was added to some cell aliquots so that the final concentration of IRM compound was 10 μM. As a positive control, some cell aliquots were incubated with Sendai virus instead of IRM compound. As a negative control, some cell aliquots were incubated with DMSO without IRM compound. In all cases, the cells were incubated for 18 hours.

Table 1 - IRM Compounds

Compound	Chemical Name	Citation
IRM 1	4-amino-2-ethoxymethyl-α,α-dimethyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol	U.S. 5,352,784 Example 91
IRM 2	4-amino-α,α,2-trimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol	U.S. 5,266,575 Example C1
IRM 3	N-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide	U.S. 6,331,539 Example 6
IRM 4	1-{2-[3-(3-pyridyl)propoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine	WO 02/46193 Example 33
IRM 5	2-butyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine	U.S. 6,194,425 Example 39
IRM 6	2-butyl-6,7,8,9-tetrahydro-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine	U.S. 6,194,425 Example 40
IRM 7	N^3-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-6-(1*H*-1-pyrrolyl)nicotinamide	U.S. 6,451,810 Example 60
IRM 8	2-ethyl-1-[5-(methylsulfonyl)pentyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine	WO 02/46192 Example 13

The plates were equilibrated to room temperature before 1 volume of reconstituted LucLight Plus (Packard Instruments, Meriden, CT) was added to each aliquot of cells. Each well of the plate was read on an LJL Analyst (LJL Biosystems, Inc., Sunnyvale, CA) set with a 5 minute dark adapt. Data from a representative experiment are shown in Table 2. The data are expressed as the fold increase in luciferase induction off of the IFN-α1 promoter in cell aliquots incubated with the indicated stimulant compared to the negative control in which the cell aliquots were incubated with only DMSO.

Table 2 - TLR Expression by pIFN-α1-luc/pCI-TLR6 Co-Transfected Namalwa cells

Stimulant	Fold Increase in Luciferase Induction
IRM1	3.6
IRM2	2.7
IRM3	2.6
IRM4	4.0
IRM5	3.2
IRM6	2.9
IRM7	3.2
IRM8	2.3
Sendai virus	2.7

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. In case of conflict, the present specification, including definitions, shall control.

Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. Illustrative embodiments and examples are provided as examples only and are not intended to limit the scope of the present invention. The scope of the invention is limited only by the claims set forth as follows.

What is Claimed is:

1. A method of detecting activation of a TLR in a cell comprising:

providing a cell culture comprising cells transfected with a nucleic acid sequence that encodes a reporter that (a) generates a detectable signal when the reporter is expressed and the cell is exposed to conditions effective for generating the detectable signal, and (b) is operably linked to an expression control sequence that is induced by activation of a TLR and comprises a cytokine promoter, a chemokine promoter, a co-stimulatory marker promoter, or a defensin promoter;

exposing the cell culture to a compound that activates a TLR;

providing conditions effective for generating the detectable signal; and

detecting the detectable signal.

2. The method of claim 1 wherein the expression control sequence comprises an IFN-α promoter.

3. The method of claim 1 wherein the detectable signal comprises luciferase activity, β-galactosidase activity, or a positive signal from an enzyme-linked immunosorbent assay.

4. The method of claim 1 wherein the cell culture comprises mammalian cells or descendents of a mammalian cell.

5. The culture cell of claim 4 wherein the cell culture comprises human cells or descendents of a human cell.

6. The method of claim 1 wherein the cells are further transfected with a second nucleic acid sequence that encodes a TLR operably linked to a second expression control sequence.

7. The method of claim 6 wherein the first nucleic acid sequence comprises the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, or a degenerate variant of any of the foregoing.

8. The method of claim 6 wherein the first nucleic acid sequence comprises a nucleotide sequence that encodes a polypeptide having the sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, or any one of the foregoing sequences with one or more conservative amino acid substitutions.

9. The method of claim 6 wherein the nucleic acid sequence that encodes the reporter and the second nucleic acid sequence are contained on a single vector.

10. The method of claim 6 wherein the nucleic acid sequence that encodes the reporter is contained on a first vector and the second nucleic acid sequence is contained on a second vector.

11. A method of identifying a TLR agonist comprising:

providing a cell culture comprising cells transfected with:

a first nucleic acid sequence that comprises a nucleotide sequence that encodes a TLR operably linked to a first expression control sequence and

a second nucleic acid sequence that encodes a reporter that (a) generates a detectable signal when the reporter is expressed and the transfected cell is exposed to conditions effective for generating the detectable signal, and (b) is operably linked to a second expression control sequence that is induced by activation of a TLR;

contacting the cell culture with a test compound;

providing conditions effective for generating the detectable signal, thereby generating a TLR-mediated detectable signal; and

identifying the compound as an agonist of the TLR if a TLR-mediated detectable signal is detected.

12. The method of claim 11 wherein the first nucleic acid sequence comprises the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, or a degenerate variant of any of the foregoing.

13. The method of claim 11 wherein the first nucleic acid sequence comprises a nucleotide sequence that encodes a polypeptide having the sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, or any one of the foregoing sequences with one or more conservative amino acid substitutions.

14. The method of claim 11 wherein the second expression control sequence comprises an IFN-α promoter.

15. The method of claim 11 wherein the detectable signal comprises luciferase activity, β-galactosidase activity, or a positive signal from an enzyme-linked immunosorbent assay.

16. The method of claim 11 wherein the cell culture comprises mammalian cells or descendents of a mammalian cell.

17. The method of claim 16 wherein the cell culture comprises human cells or descendents of a human cell.

18. The method of claim 11 wherein the first nucleic acid sequence and the second nucleic acid sequence are included in a single vector.

19. The method of claim 11 wherein the first nucleic acid sequence and the second nucleic acid sequence are located on separate vectors.

20. The method of claim 19 wherein the cell culture comprises cells co-transfected with the separate vectors.

21. The method of claim 11 wherein the cell culture comprises cells that, prior to transfection with the first nucleic acid sequence, exhibit no detectable function of the Toll-like receptor encoded by the first nucleic acid sequence.

22. The method of claim 11 wherein the second expression control sequence comprises a cytokine promoter, a chemokine promoter, a co-stimulatory marker promoter, or a defensin promoter

23. A TLR agonist identified by the method of claim 11.

24. A pharmaceutical composition comprising a TLR agonist identified by the method of claim 23 or a pharmaceutically acceptable salt thereof.

25. A method of identifying an antagonist of a TLR comprising:

providing a cell culture that comprises cells transfected with:

a first nucleic acid sequence that comprises a nucleotide sequence that encodes the TLR operably linked to a first expression control sequence, and

a second nucleic acid sequence that encodes a reporter that (a) is operably linked to a second expression control sequence that is induced by activation of the TLR, and (b) generates a detectable signal when the reporter is expressed and the transfected cell is exposed to conditions effective for generating the detectable signal;

contacting the cell culture with an agonist of the TLR and a test compound;

providing conditions effective for generating the detectable signal, thereby permitting the cell culture to generate a full TLR-mediated detectable signal in the absence of an antagonist of the TLR;

measuring the detectable signal; and

identifying the compound as an antagonist of the TLR if the detectable signal is less than a full TLR-mediated detectable signal.

26. A TLR antagonist identified by the method of claim 25.

27. A pharmaceutical composition comprising a TLR antagonist identified by the method of claim 26 or a pharmaceutically acceptable salt thereof.

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Asn Gly Ile Cys Lys Gly Ser Ser Gly Ser Leu Asn Ser Ile Pro Ser
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Gly Leu Thr Glu Ala Val Lys Ser Leu Asp Leu Ser Asn Asn Arg Ile
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Ser Ser Leu Gly Ser Leu Glu His Leu Asp Leu Ser Tyr Asn Tyr Leu
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Ser Asn Leu Ser Ser Ser Trp Phe Lys Pro Leu Ser Ser Leu Thr Phe
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Leu Asn Leu Leu Gly Asn Pro Tyr Lys Thr Leu Gly Glu Thr Ser Leu
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Phe Ser His Leu Thr Lys Leu Gln Ile Leu Arg Val Gly Asn Met Asp
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Thr Phe Thr Lys Ile Gln Arg Lys Asp Phe Ala Gly Leu Thr Phe Leu
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Glu Glu Leu Glu Ile Asp Ala Ser Asp Leu Gln Ser Tyr Glu Pro Lys
180 185 190

Ser Leu Lys Ser Ile Gln Asn Val Ser His Leu Ile Leu His Met Lys
195 200 205

Gln His Ile Leu Leu Leu Glu Ile Phe Val Asp Val Thr Ser Ser Val
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Cys Leu Leu Ser Gln His Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser
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Ala Trp Pro Ser Leu Gln Thr Leu Ile Leu Arg Gln Asn His Leu Ala
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Ser Leu Glu Lys Thr Gly Glu Thr Leu Leu Thr Leu Lys Asn Leu Thr
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Asn Ile Asp Ile Ser Lys Asn Ser Phe His Ser Met Pro Glu Thr Cys
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Glu Ala Gly Gly Asn Asn Phe Ile Cys Ser Cys Glu Phe Leu Ser Phe
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Asn Tyr Leu Cys Asp Ser Pro Ser His Val Arg Gly Gln Gln Val Gln
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Cys His Arg Phe His Gly Leu Trp Tyr Met Lys Met Met Trp Ala Trp
610 615 620

Leu Gln Ala Lys Arg Lys Pro Arg Lys Ala Pro Ser Arg Asn Ile Cys
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Tyr Asp Ala Phe Val Ser Tyr Ser Glu Arg Asp Ala Tyr Trp Val Glu
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Asn Leu Met Val Gln Glu Leu Glu Asn Phe Asn Pro Pro Phe Lys Leu
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Cys Leu His Lys Arg Asp Phe Ile Pro Gly Lys Trp Ile Ile Asp Asn
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Ile Ile Asp Ser Ile Glu Lys Ser His Lys Thr Val Phe Val Leu Ser
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Glu Asn Phe Val Lys Ser Glu Trp Cys Lys Tyr Glu Leu Asp Phe Ser
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His Phe Arg Leu Phe Asp Glu Asn Asn Asp Ala Ala Ile Leu Ile Leu
725 730 735

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Arg Leu Pro Ala Ala Asn Phe Thr Arg Tyr Ser Gln Leu Thr Ser Leu
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Lys Leu Pro Met Leu Lys Val Leu Asn Leu Gln His Asn Glu Leu Ser
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Gln Leu Ser Asp Lys Thr Phe Ala Phe Cys Thr Asn Leu Thr Glu Leu
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His Leu Met Ser Asn Ser Ile Gln Lys Ile Lys Asn Asn Pro Phe Val
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Lys Gln Lys Asn Leu Ile Thr Leu Asp Leu Ser His Asn Gly Leu Ser
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Ser Thr Lys Leu Gly Thr Gln Val Gln Leu Glu Asn Leu Gln Glu Leu
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Leu Leu Ser Asn Asn Lys Ile Gln Ala Leu Lys Ser Glu Glu Leu Asp
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Ile Phe Ala Asn Ser Ser Leu Lys Lys Leu Glu Leu Ser Ser Asn Gln
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Leu Cys Leu Glu Leu Ala Asn Thr Ser Ile Arg Asn Leu Ser Leu Ser
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Asn Ser Gln Leu Ser Thr Thr Ser Asn Thr Thr Phe Leu Gly Leu Lys
            260                 265                 270

Trp Thr Asn Leu Thr Met Leu Asp Leu Ser Tyr Asn Asn Leu Asn Val
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Val Gly Asn Asp Ser Phe Ala Trp Leu Pro Gln Leu Glu Tyr Phe Phe
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Leu Glu Tyr Asn Asn Ile Gln His Leu Phe Ser His Ser Leu His Gly
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Leu Phe Asn Val Arg Tyr Leu Asn Leu Lys Arg Ser Phe Thr Lys Gln
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Asn Lys Ile Ser Lys Ile Glu Ser Asp Ala Phe Ser Trp Leu Gly His
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Leu Ser His Leu His Ile Leu Asn Leu Glu Ser Asn Gly Phe Asp Glu
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Val Glu Lys Lys Val Phe Gly Pro Ala Phe Arg Asn Leu Thr Glu Leu
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Asp Met Arg Phe Asn Pro Phe Asp Cys Thr Cys Glu Ser Ile Ala Trp
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Phe Val Asn Trp Ile Asn Glu Thr His Thr Asn Ile Pro Glu Leu Ser
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Ser His Tyr Leu Cys Asn Thr Pro Pro His Tyr His Gly Phe Pro Val
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Arg Leu Phe Asp Thr Ser Ser Cys Lys Asp Ser Ala Pro Phe Glu Leu
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Phe Phe Met Ile Asn Thr Ser Ile Leu Leu Ile Phe Ile Phe Ile Val
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Leu Leu Ile His Phe Glu Gly Trp Arg Ile Ser Phe Tyr Trp Asn Val
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Ser Val His Arg Val Leu Gly Phe Lys Glu Ile Asp Arg Gln Thr Glu
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Gln Phe Glu Tyr Ala Ala Tyr Ile Ile His Ala Tyr Lys Asp Lys Asp
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Trp Val Trp Glu His Phe Ser Ser Met Glu Lys Glu Asp Gln Ser Leu
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Lys Phe Cys Leu Glu Glu Arg Asp Phe Glu Ala Gly Val Phe Glu Leu
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Glu Ala Ile Val Asn Ser Ile Lys Arg Ser Arg Lys Ile Ile Phe Val
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Ile Thr His His Leu Leu Lys Asp Pro Leu Cys Lys Arg Phe Lys Val
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Leu Val Phe Leu Glu Glu Ile Pro Asp Tyr Lys Leu Asn His Ala Leu
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Cys Leu Arg Arg Gly Met Phe Lys Ser His Cys Ile Leu Asn Trp Pro
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<213> Homo sapiens

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Ser Phe Phe Ser Phe Pro Glu Leu Gln Val Leu Asp Leu Ser Arg Cys
35 40 45

Glu Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu Ser His Leu
50 55 60

Ser Thr Leu Ile Leu Thr Gly Asn Pro Ile Gln Ser Leu Ala Leu Gly
65 70 75 80

Ala Phe Ser Gly Leu Ser Ser Leu Gln Lys Leu Val Ala Val Glu Thr
85 90 95

Asn Leu Ala Ser Leu Glu Asn Phe Pro Ile Gly His Leu Lys Thr Leu
100 105 110

Lys Glu Leu Asn Val Ala His Asn Leu Ile Gln Ser Phe Lys Leu Pro
115 120 125

Glu Tyr Phe Ser Asn Leu Thr Asn Leu Glu His Leu Asp Leu Ser Ser
130 135 140

Asn Lys Ile Gln Ser Ile Tyr Cys Thr Asp Leu Arg Val Leu His Gln
145 150 155 160

Met Pro Leu Leu Asn Leu Ser Leu Asp Leu Ser Leu Asn Pro Met Asn
165 170 175

Phe Ile Gln Pro Gly Ala Phe Lys Glu Ile Arg Leu His Lys Leu Thr
180 185 190

Leu Arg Asn Asn Phe Asp Ser Leu Asn Val Met Lys Thr Cys Ile Gln
195 200 205

Gly Leu Ala Gly Leu Glu Val His Arg Leu Val Leu Gly Glu Phe Arg
210 215 220

Asn Glu Gly Asn Leu Glu Lys Phe Asp Lys Ser Ala Leu Glu Gly Leu
225 230 235 240

Cys Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu Asp Tyr Tyr
245 250 255

Leu Asp Asp Ile Ile Asp Leu Phe Asn Cys Leu Thr Asn Val Ser Ser
260 265 270

Phe Ser Leu Val Ser Val Thr Ile Glu Arg Val Lys Asp Phe Ser Tyr
275 280 285

Asn Phe Gly Trp Gln His Leu Glu Leu Val Asn Cys Lys Phe Gly Gln
290 295 300

Phe Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr Phe Thr Ser
305 310 315 320

Asn Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro Ser Leu Glu
325 330 335

Phe Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly Cys Cys Ser
340 345 350

Gln Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp Leu Ser Phe

355 360 365

Asn Gly Val Ile Thr Met Ser Ser Asn Phe Leu Gly Leu Glu Gln Leu
370 375 380

Glu His Leu Asp Phe Gln His Ser Asn Leu Lys Gln Met Ser Glu Phe
385 390 395 400

Ser Val Phe Leu Ser Leu Arg Asn Leu Ile Tyr Leu Asp Ile Ser His
405 410 415

Thr His Thr Arg Val Ala Phe Asn Gly Ile Phe Asn Gly Leu Ser Ser
420 425 430

Leu Glu Val Leu Lys Met Ala Gly Asn Ser Phe Gln Glu Asn Phe Leu
435 440 445

Pro Asp Ile Phe Thr Glu Leu Arg Asn Leu Thr Phe Leu Asp Leu Ser
450 455 460

Gln Cys Gln Leu Glu Gln Leu Ser Pro Thr Ala Phe Asn Ser Leu Ser
465 470 475 480

Ser Leu Gln Val Leu Asn Met Ser His Asn Asn Phe Phe Ser Leu Asp
485 490 495

Thr Phe Pro Tyr Lys Cys Leu Asn Ser Leu Gln Val Leu Asp Tyr Ser
500 505 510

Leu Asn His Ile Met Thr Ser Lys Lys Gln Glu Leu Gln His Phe Pro
515 520 525

Ser Ser Leu Ala Phe Leu Asn Leu Thr Gln Asn Asp Phe Ala Cys Thr
530 535 540

Cys Glu His Gln Ser Phe Leu Gln Trp Ile Lys Asp Gln Arg Gln Leu
545 550 555 560

Leu Val Glu Val Glu Arg Met Glu Cys Ala Thr Pro Ser Asp Lys Gln
565 570 575

Gly Met Pro Val Leu Ser Leu Asn Ile Thr Cys Gln Met Asn Lys Thr
580 585 590

Ile Ile Gly Val Ser Val Leu Ser Val Leu Val Val Ser Val Val Ala
595 600 605

Val Leu Val Tyr Lys Phe Tyr Phe His Leu Met Leu Leu Ala Gly Cys
610 615 620

Ile Lys Tyr Gly Arg Gly Glu Asn Ile Tyr Asp Ala Phe Val Ile Tyr
625 630 635 640

Ser Ser Gln Asp Glu Asp Trp Val Arg Asn Glu Leu Val Lys Asn Leu
645 650 655

Glu Glu Gly Val Pro Pro Phe Gln Leu Cys Leu His Tyr Arg Asp Phe
660 665 670

Ile Pro Gly Val Ala Ile Ala Ala Asn Ile Ile His Glu Gly Phe His
675 680 685

Lys Ser Arg Lys Val Ile Val Val Val Ser Gln His Phe Ile Gln Ser
690 695 700

Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala Gln Thr Trp Gln Phe Leu
705 710 715 720

Ser Ser Arg Ala Gly Ile Ile Phe Ile Val Leu Gln Lys Val Glu Lys
725 730 735

Thr Leu Leu Arg Gln Gln Val Glu Leu Tyr Arg Leu Leu Ser Arg Asn
740 745 750

Thr Tyr Leu Glu Trp Glu Asp Ser Val Leu Gly Arg His Ile Phe Trp
755 760 765

Arg Arg Leu Arg Lys Ala Leu Leu Asp Gly Lys Ser Trp Asn Pro Glu
770 775 780

Gly Thr Val Gly Thr Gly Cys Asn Trp Gln Glu Ala Thr Ser Ile
785 790 795

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<212> DNA
<213> Homo sapiens

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Glu Pro Asp Met Tyr Lys Tyr Asp Ala Tyr Leu Cys Phe Ser Ser Lys
        35                  40                  45

Asp Phe Thr Trp Val Gln Asn Ala Leu Leu Lys His Leu Asp Thr Gln
    50                  55                  60

Tyr Ser Asp Gln Asn Arg Phe Asn Leu Cys Phe Glu Glu Arg Asp Phe
65                  70                  75                  80
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Val Pro Gly Glu Asn Arg Ile Ala Asn Ile Gln Asp Ala Ile Trp Asn
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Ser Arg Lys Ile Val Cys Leu Val Ser Arg His Phe Leu Arg Asp Gly
100 105 110

Trp Cys Leu Glu Ala Phe Ser Tyr Ala Gln Gly Arg Cys Leu Ser Asp
115 120 125

Leu Asn Ser Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln Tyr
130 135 140

Gln Leu Met Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln Gln
145 150 155 160

Tyr Leu Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu His
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Lys Leu Ser Gln Gln Ile Leu Lys Lys Glu Lys Glu Lys Lys Lys Asp
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Asn Asn Ile Pro Leu Gln Thr Val Ala Thr Ile Ser
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aaccaggatt tagaatattt ggatttatct cataatcagt tgcaaaagat atcctgccat 420

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agaaattatt atataaaaga aaatgagaca gaaagtctac aaattctgaa tgcaaaaacc 660

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<211> 796
<212> PRT
<213> Homo sapiens

<400> 12

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Glu Phe Ala Val Asp Lys Ser Lys Arg Gly Leu Ile His Val Pro Lys
35 40 45

Asp Leu Pro Leu Lys Thr Lys Val Leu Asp Met Ser Gln Asn Tyr Ile
50 55 60

Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu Thr Val
65 70 75 80

Leu Arg Leu Ser His Asn Arg Ile Gln Leu Leu Asp Leu Ser Val Phe
85 90 95

Lys Phe Asn Gln Asp Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu
100 105 110

Gln Lys Ile Ser Cys His Pro Ile Val Ser Phe Arg His Leu Asp Leu
115 120 125

Ser Phe Asn Asp Phe Lys Ala Leu Pro Ile Cys Lys Glu Phe Gly Asn
130 135 140

Leu Ser Gln Leu Asn Phe Leu Gly Leu Ser Ala Met Lys Leu Gln Lys
145 150 155 160

Leu Asp Leu Leu Pro Ile Ala His Leu His Leu Ser Tyr Ile Leu Leu
165 170 175

Asp Leu Arg Asn Tyr Tyr Ile Lys Glu Asn Glu Thr Glu Ser Leu Gln
180 185 190

Ile Leu Asn Ala Lys Thr Leu His Leu Val Phe His Pro Thr Ser Leu
195 200 205

Phe Ala Ile Gln Val Asn Ile Ser Val Asn Thr Leu Gly Cys Leu Gln
210 215 220

Leu Thr Asn Ile Lys Leu Asn Asp Asp Asn Cys Gln Val Phe Ile Lys
225 230 235 240

Phe Leu Ser Glu Leu Thr Arg Gly Ser Thr Leu Leu Asn Phe Thr Leu
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Asn His Ile Glu Thr Thr Trp Lys Cys Leu Val Arg Val Phe Gln Phe
260 265 270

Leu Trp Pro Lys Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile
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Ile Glu Ser Ile Arg Glu Glu Asp Phe Thr Tyr Ser Lys Thr Thr Leu
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Lys Ala Leu Thr Ile Glu His Ile Thr Asn Gln Val Phe Leu Phe Ser
305 310 315 320

Gln Thr Ala Leu Tyr Thr Val Phe Ser Glu Met Asn Ile Met Met Leu
325 330 335

Thr Ile Ser Asp Thr Pro Phe Ile His Met Leu Cys Pro His Ala Pro
340 345 350

Ser Thr Phe Lys Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser
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Ile Phe Glu Lys Cys Ser Thr Leu Val Lys Leu Glu Thr Leu Ile Leu
370 375 380

Gln Lys Asn Gly Leu Lys Asp Leu Phe Lys Val Gly Leu Met Thr Lys
385 390 395 400

Asp Met Pro Ser Leu Glu Ile Leu Asp Val Ser Trp Asn Ser Leu Glu
405 410 415

Ser Gly Arg His Lys Glu Asn Cys Thr Trp Val Glu Ser Ile Val Val
420 425 430

Leu Asn Leu Ser Ser Asn Met Leu Thr Asp Ser Val Phe Arg Cys Leu
435 440 445

Pro Pro Arg Ile Lys Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser
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Val Pro Lys Gln Val Val Lys Leu Glu Ala Leu Gln Glu Leu Asn Val
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Ala Phe Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ser Phe Ser Ser
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Leu Ser Val Leu Ile Ile Asp His Asn Ser Val Ser His Pro Ser Ala
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Asp Phe Phe Gln Ser Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp
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Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Glu Phe Val Lys Asn Ile
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Asp Gln Val Ser Ser Glu Val Leu Glu Gly Trp Pro Asp Ser Tyr Lys
545 550 555 560

Cys Asp Tyr Pro Glu Ser Tyr Arg Gly Ser Pro Leu Lys Asp Phe His
565 570 575

Met Ser Glu Leu Ser Cys Asn Ile Thr Leu Leu Ile Val Thr Ile Gly
580 585 590

Ala Thr Met Leu Val Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr
595 600 605

Leu Asp Leu Pro Trp Tyr Leu Arg Met Val Cys Gln Trp Thr Gln Thr
610 615 620

Arg Arg Arg Ala Arg Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu
625 630 635 640

Gln Phe His Ala Phe Ile Ser Tyr Ser Glu His Asp Ser Ala Trp Val
645 650 655

Lys Ser Glu Leu Val Pro Tyr Leu Glu Lys Glu Asp Ile Gln Ile Cys
660 665 670

Leu His Glu Arg Asn Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile
675 680 685

Ile Asn Cys Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro
690 695 700

Asn Phe Val Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His

705 710 715 720

His Asn Leu Phe His Glu Gly Ser Asn Asn Leu Ile Leu Ile Leu Leu
725 730 735

Glu Pro Ile Pro Gln Asn Ser Ile Pro Asn Lys Tyr His Lys Leu Lys
740 745 750

Ala Leu Met Thr Gln Arg Thr Tyr Leu Gln Trp Pro Lys Glu Lys Ser
755 760 765

Lys Arg Gly Leu Phe Trp Ala Asn Ile Arg Ala Ala Phe Asn Met Lys
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Leu Thr Leu Val Thr Glu Asn Asn Asp Val Lys Ser
785 790 795

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<211> 5007
<212> DNA
<213> Homo sapiens

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Arg Cys Asn Cys Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys
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Phe Ser Ile Arg Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile
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Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser
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Tyr Ser Ile Glu Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val
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Gln Glu Asp Asp Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu
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Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro
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Cys Lys Asn Asn Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala
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Val Pro Pro Arg Trp Phe Lys Asn Ile Asn Lys Leu Gln Glu Leu Asp
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Leu Ser Gln Asn Phe Leu Ala Lys Glu Ile Gly Asp Ala Lys Phe Leu
325 330 335

His Phe Leu Pro Ser Leu Ile Gln Leu Asp Leu Ser Phe Asn Phe Glu
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Leu Gln Val Tyr Arg Ala Ser Met Asn Leu Ser Gln Ala Phe Ser Ser
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370 375 380

Leu Lys Ser Phe Asn Leu Ser Pro Leu His Asn Leu Gln Asn Leu Glu
385 390 395 400

Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asn Leu Ser Met
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Phe Lys Gln Phe Lys Arg Leu Lys Val Ile Asp Leu Ser Val Asn Lys
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Ile Ser Pro Ser Gly Asp Ser Ser Glu Val Gly Phe Cys Ser Asn Ala
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Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn Leu
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Ile Ser Gln Thr Leu Asn Gly Ser Glu Phe Gln Pro Leu Ala Glu Leu
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Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu His Ser Thr
545 550 555 560

Ala Phe Glu Glu Leu His Lys Leu Glu Val Leu Asp Ile Ser Ser Asn
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Ser His Tyr Phe Gln Ser Glu Gly Ile Thr His Met Leu Asn Phe Thr
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Lys Asn Leu Lys Val Leu Gln Lys Leu Met Met Asn Asp Asn Asp Ile
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Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Glu Gly Asp Asn
625 630 635 640

Arg Tyr Leu Gln Leu Phe Lys Asn Leu Leu Lys Leu Glu Glu Leu Asp
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Thr Glu Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val Gly
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Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr Thr
820 825 830

Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Leu Ser Ile Ser
835 840 845

Val Ser Leu Phe Leu Met Val Met Met Thr Ala Ser His Leu Tyr Phe
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Trp Asp Val Trp Tyr Ile Tyr His Phe Cys Lys Ala Lys Ile Lys Gly
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Tyr Gln Arg Leu Ile Ser Pro Asp Cys Cys Tyr Asp Ala Phe Ile Val
885 890 895

Tyr Asp Thr Lys Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu
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Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu
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Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu Ser
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Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly Lys Tyr
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Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile Val Ser
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Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu Arg Leu
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Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn
50 55 60

Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp
65 70 75 80

Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp
85 90 95

Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met
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Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu
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Leu Ile Ser Leu Ser Leu Ser His Thr Asn Ile Leu Met Leu Asp Ser
145   150   155   160

Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly
                165   170   175

Asn Cys Tyr Tyr Lys Asn Pro Cys Arg Gln Ala Leu Glu Val Ala Pro
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Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
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Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr
    210   215   220

Leu Leu Leu Ser Tyr Asn Arg Ile Val Lys Leu Ala Pro Glu Asp Leu
225   230   235   240

Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
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Arg Cys Asp His Ala Pro Asn Pro Cys Met Glu Cys Pro Arg His Phe
            260   265   270

Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly
        275   280   285

Leu Val Leu Lys Asp Ser Ser Leu Ser Trp Leu Asn Ala Ser Trp Phe
    290   295   300

Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu
305   310   315   320

Tyr Lys Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Thr Gln Leu
                325   330   335

Arg Lys Leu Asn Leu Ser Phe Asn Tyr Gln Lys Arg Val Ser Phe Ala
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His Leu Ser Leu Ala Pro Ser Phe Gly Ser Leu Val Ala Leu Lys Glu
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Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Asp Glu Thr Thr Leu
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Arg Pro Leu Ala Arg Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met
385 390 395 400

Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Arg Ala Phe Pro Gly
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Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ser Glu
420 425 430

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Gln Pro Gly Asp Leu Ala Pro Ala Pro Val Asp Thr Pro Ser Ser Glu
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Asp Phe Arg Pro Asn Cys Ser Thr Leu Asn Phe Thr Leu Asp Leu Ser
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Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser
485 490 495

His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val
500 505 510

Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu
515 520 525

Ser Arg Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu
530 535 540

Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly
545 550 555 560

Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr
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Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser
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Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn

595 600 605

Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe
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Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu
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His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln
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Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser
660 665 670

Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Arg
675 680 685

Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg
690 695 700

Arg Leu Asp Val Ser Cys Asn Ser Ile Ser Phe Val Ala Pro Gly Phe
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Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala
725 730 735

Leu Lys Thr Val Asp His Ser Trp Phe Gly Pro Leu Ala Ser Ala Leu
740 745 750

Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala
755 760 765

Ala Phe Met Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu
770 775 780

Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Leu Ser
785 790 795 800

Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp
805 810 815

Asp Cys Phe Ala Leu Ser Leu Leu Ala Val Ala Leu Gly Leu Gly Val
820 825 830

Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His
835 840 845

Leu Cys Leu Ala Trp Leu Pro Trp Arg Gly Arg Gln Ser Gly Arg Asp
850 855 860

Glu Asp Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Thr Gln
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Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Gly Gln Leu Glu
885 890 895

Glu Cys Arg Gly Arg Trp Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp
900 905 910

Trp Leu Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr
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Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
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Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
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Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Ser Pro Asp Gly Arg
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Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
980 985 990

Leu Leu Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln
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35 40 45

Ala Thr Thr Thr Leu Asp Leu Ser Tyr Asn Leu Leu Phe Gln Leu Gln
50 55 60

Ser Ser Asp Phe His Ser Val Ser Lys Leu Arg Val Leu Ile Leu Cys
65 70 75 80

His Asn Arg Ile Gln Gln Leu Asp Leu Lys Thr Phe Glu Phe Asn Lys
85 90 95

Glu Leu Arg Tyr Leu Asp Leu Ser Asn Asn Arg Leu Lys Ser Val Thr

100 105 110

Trp Tyr Leu Leu Ala Gly Leu Arg Tyr Leu Asp Leu Ser Phe Asn Asp
115 120 125

Phe Asp Thr Met Pro Ile Cys Glu Glu Ala Gly Asn Met Ser His Leu
130 135 140

Glu Ile Leu Gly Leu Ser Gly Ala Lys Ile Gln Lys Ser Asp Phe Gln
145 150 155 160

Lys Ile Ala His Leu His Leu Asn Thr Val Phe Leu Gly Phe Arg Thr
165 170 175

Leu Pro His Tyr Glu Glu Gly Ser Leu Pro Ile Leu Asn Thr Thr Lys
180 185 190

Leu His Ile Val Leu Pro Met Asp Thr Asn Phe Trp Val Leu Leu Arg
195 200 205

Asp Gly Ile Lys Thr Ser Lys Ile Leu Glu Met Thr Asn Ile Asp Gly
210 215 220

Lys Ser Gln Phe Val Ser Tyr Glu Met Gln Arg Asn Leu Ser Leu Glu
225 230 235 240

Asn Ala Lys Thr Ser Val Leu Leu Leu Asn Lys Val Asp Leu Leu Trp
245 250 255

Asp Asp Leu Phe Leu Ile Leu Gln Phe Val Trp His Thr Ser Val Glu
260 265 270

His Phe Gln Ile Arg Asn Val Thr Phe Gly Gly Lys Ala Tyr Leu Asp
275 280 285

His Asn Ser Phe Asp Tyr Ser Asn Thr Val Met Arg Thr Ile Lys Leu
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Glu His Val His Phe Arg Val Phe Tyr Ile Gln Gln Asp Lys Ile Tyr
305 310 315 320

Leu Leu Leu Thr Lys Met Asp Ile Glu Asn Leu Thr Ile Ser Asn Ala
325 330 335

Gln Met Pro His Met Leu Phe Pro Asn Tyr Pro Thr Lys Phe Gln Tyr
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Glu Thr Leu Ser Leu Val Ser Cys Phe Ala Asn Asn Thr Pro Leu Glu
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His Leu Asp Leu Ser Gln Asn Leu Leu Gln His Lys Asn Asp Glu Asn
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Cys Ser Trp Pro Glu Thr Val Val Asn Met Asn Leu Ser Tyr Asn Lys
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Leu Ser Asp Ser Val Phe Arg Cys Leu Pro Lys Ser Ile Gln Ile Leu
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Asp Leu Asn Asn Asn Gln Ile Gln Thr Val Pro Lys Glu Thr Ile His
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Leu Met Ala Leu Arg Glu Leu Asn Ile Ala Phe Asn Phe Leu Thr Asp
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Leu Pro Gly Cys Ser His Phe Ser Arg Leu Ser Val Leu Asn Ile Glu
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Glu Val Lys Thr Leu Asn Ala Gly Arg Asn Pro Phe Arg Cys Thr Cys
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Glu Leu Lys Asn Phe Ile Gln Leu Glu Thr Tyr Ser Glu Val Met Met
    530                 535                 540

Val Gly Trp Ser Asp Ser Tyr Thr Cys Glu Tyr Pro Leu Asn Leu Arg
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Gly Ile Arg Leu Lys Asp Val His Leu His Glu Leu Ser Cys Asn Thr
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Ala Leu Leu Ile Val Thr Ile Val Val Ile Met Leu Val Leu Gly Leu
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Ala Val Ala Phe Cys Cys Leu His Phe Asp Leu Pro Trp Tyr Leu Arg
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Gln Glu Gln Leu Lys Arg Asn Val Arg Phe His Ala Phe Ile Ser Tyr
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Ser Glu His Asp Ser Leu Trp Val Lys Asn Glu Leu Ile Pro Asn Leu
645 650 655

Glu Lys Glu Asp Gly Ser Ile Leu Ile Cys Leu Tyr Glu Ser Tyr Phe
660 665 670

Asp Pro Gly Lys Ser Ile Ser Glu Asn Ile Val Ser Phe Ile Glu Lys
675 680 685

Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Asn Glu
690 695 700

Trp Cys His Tyr Glu Phe Tyr Phe Ala His His Asn Leu Phe His Glu
705 710 715 720

Asn Ser Asp His Ile Ile Leu Ile Leu Leu Glu Pro Ile Pro Phe Tyr
725 730 735

Cys Ile Pro Thr Arg Tyr His Lys Leu Lys Ala Leu Leu Glu Lys Lys
740 745 750

Ala Tyr Leu Glu Trp Pro Lys Asp Arg Arg Lys Cys Gly Leu Phe Trp
755 760 765

Ala Asn Leu Arg Ala Ala Ile Asn Val Asn Val Leu Ala Thr Arg Glu
770 775 780

Met Tyr Glu Leu Gln Thr Phe Thr Glu Leu Asn Glu Glu Ser Arg Gly
785 790 795 800

Ser Thr Ile Ser Leu Met Arg Thr Asp Cys Leu
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